

Treatment of chancroid with erythromycin

A clinical and microbiological appraisal

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SUMMARY One hundred and thirty seven patients presenting with genital ulcerations from which *Haemophilus ducreyi* was isolated were treated with erythromycin stearate 500 mg every six hours for seven days. Of these, 91 (66%) had associated inguinal lymphadenopathy. Only two of the 100 patients who returned after one week showed no clinical improvement. Despite decrease in size *H ducreyi* was reisolated from the ulcers of three patients, two of whom had not complied with treatment. The patients were treated for a further week either with erythromycin or with a placebo preparation and on day 14 no discernible difference in clinical response was evident. *H ducreyi* was not reisolated from any lesion. In contrast, the natural course of development of associated lymphadenopathy was not modified by treatment. *H ducreyi* was not, however, isolated from any gland after the start of treatment. Side effects attributable to erythromycin were minimal and treatment had to be discontinued in only two patients. This study clearly indicates that treatment with erythromycin for one week results in rapid healing of lesions and the elimination of *H ducreyi* from both ulcers and associated lymph glands.

Introduction

Chancroid, a sexually transmitted disease caused by *Haemophilus ducreyi*, is endemic in many tropical and subtropical countries, but outbreaks of the disease have recently occurred in more temperate climates. In Johannesburg chancroid has recently been recognised as the most common cause of genital ulceration in black men, *H ducreyi* being isolated in 62 of 102 (61%) of unselected cases.¹ Most isolates produced β -lactamase and were, therefore, resistant to penicillin. In addition, in vitro resistance to the antimicrobial agents usually recommended for the treatment of chancroid—namely, the sulphonamides ($MIC_{90} > 128 \mu\text{g/ml}$) and tetracycline ($MIC_{90} 16 \mu\text{g/ml}$)—was found.² In contrast the in vitro susceptibility of these isolates to erythromycin ($MIC_{90} 0.03 \mu\text{g/ml}$) indicated that this antibiotic should be effective in treating chancroid in southern Africa. Recently, Carpenter and his colleagues in the United States reported the successful treatment with

erythromycin of seven cases of chancroid, all of which had been acquired in Korea.³

In this study we assessed the clinical and microbiological response of a large number of cases of chancroid to treatment with erythromycin and undertook initial attempts to determine the optimum duration of treatment.

Patients and methods

Both men and women presenting with painful genital ulcers consistent with a clinical diagnosis of chancroid were included in the study. All patients were examined at the outpatient department, Hillbrow Hospital, Johannesburg, between August 1980 and February 1982. After a detailed history had been obtained the number, size, site, and clinical features of genital lesions were recorded. The presence of pronounced tender inguinal lymphadenopathy ($\geq 15 \text{ mm}$) with or without abscess formation was also noted.

SPECIMEN COLLECTION

In each patient the largest active ulcer was selected for investigation. After thorough cleansing serous material was collected from the base of lesions with a platinum scraper (Kimura spatula, Storz

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Instruments, St Louis, Missouri, USA) and examined by darkfield microscopy for evidence of infection with *Treponema pallidum*. Material from the base of each target lesion was collected with three calcium alginate swabs (Calgiswab, code No 60-150-28, Inolex Corporation, Glenwood, Illinois, USA), which were used at random for the isolation of *H ducreyi*, *Chlamydia trachomatis*, and *Herpesvirus hominis* (HVH).

CULTURE TECHNIQUES

Isolation of *H ducreyi* was performed using a modification of the technique described by Hammond *et al.*⁴ The material was inoculated directly on to a solid medium comprising Mueller-Hinton agar base (Baltimore Biological Laboratory, Cockeysville, Maryland, USA), 5% sterile horse blood heated to 75°C, 1% IsoVitaleX (Baltimore Biological Laboratory, Cockeysville, Maryland, USA) and 3 µg/ml vancomycin (Eli Lilly & Co, Indianapolis, Indiana, USA). Inoculated plates were placed in a candle extinction jar at room temperature for up to six hours, after which they were transferred to a microaerophilic atmosphere provided by an anaerobic jar from which the catalyst had been removed, and incubated at 35°C for 48-72 hours. Typical colonies of *H ducreyi* which could be pushed intact across the agar surface were sought and their identity confirmed according to the criteria of Killian.⁵

Attempts to isolate *C trachomatis* and HVH were made using cycloheximide-treated McCoy cells⁶ and human embryo lung fibroblasts respectively.

Where applicable isolation of *H ducreyi* and *C trachomatis* was attempted from aspirates obtained from fluctuant inguinal lymph glands and material from draining sinuses (where the glands had ruptured spontaneously). In all cases blood specimens obtained by venepuncture were tested for antichlamydial antibody by a modified microimmunofluorescence technique⁷ and for syphilis by the rapid plasma reagin (RPR) and fluorescent treponemal antibody-absorbed (FTA-ABS) tests.

Patients were excluded from the study if darkfield examination was positive for syphilis, if *C trachomatis* or HVH was isolated retrospectively from the lesions, or if attempts to culture *H ducreyi* were unsuccessful. Serological evidence alone of syphilis or lymphogranuloma venereum infection (microimmunofluorescence titres ≥ 256) was not a criterion for exclusion, provided that *H ducreyi* was isolated from the ulcer.

TREATMENT AND FOLLOW UP

All patients in the study were treated initially with erythromycin stearate 500 mg by mouth every six

hours for seven days. Subsequently, patients were treated with erythromycin stearate at the same dosage either for a further week or until their lesions had healed completely. A group of patients was given placebo tablets every six hours after completion of one week's treatment with erythromycin. All patients were requested to return for reassessment on day 7, day 14, and if not completely cured on day 21. Cultures for isolation of *H ducreyi* were repeated at follow up if the target ulcer had not re-epithelialised, if the lymph glands had become fluctuant, or if a draining sinus had formed or persisted.

Results

INITIAL VISIT

During the study period 210 patients with lesions clinically resembling those of chancroid were initially admitted to the study. Of these, however, HVH was isolated from the lesions of eight (six of which also yielded *H ducreyi* on culture). Evidence of lymphogranuloma venereum was obtained in two cases, both by culture of *C trachomatis*, and syphilis was subsequently diagnosed by serology in four cases. In 59 cases *H ducreyi* was not isolated in culture, and all other laboratory investigations were negative. Of the remaining 137 cases, all of which were *H ducreyi*-positive, serum from 29 were positive by the RPR and FTA-ABS tests and 30 positive by the FTA-ABS test only. Of these 137 patients (112 men and 25 women) who fulfilled the criteria for entry into the study, 76 (55%) had received some form of treatment in the month before their initial visit. In 59 (78%) cases treatment had been in the form of injections, presumably of penicillin.

Of the 137 patients admitted to the study, single lesions were noted in 45 (33%); their size varied from 2 to 60 mm in diameter. Phimosis, as a direct result of chancroid infection, was present in 28 of 112 (25%) men. Initially, 91 (66%) patients presented with notable painful inguinal lymphadenopathy, which was unilateral in 71 and bilateral in 20.

Inguinal abscess formation was evident in 18 patients, in 10 of which the abscesses had already ruptured and formed draining sinuses. While *H ducreyi* was isolated from all target lesions, these organisms were also isolated from seven of the 10 draining sinuses and from four of eight specimens obtained by aspiration of material from suppurating lymph nodes before treatment was started.

RESPONSE OF GENITAL ULCERS

Of the 137 patients who fulfilled the entry criteria, 100 returned for follow up examination on day 7 (see table 1). In 42 patients the lesions had completely epithelialised and in 56 the ulcers had decreased in

TABLE I Clinical response of chancroid (genital ulcers) to treatment with erythromycin

			Clinical response of lesions to treatment:						
Treatment (duration in days)	No (%) of patients returning		Epithelialised		Improved		Unchanged or worse		No (%) of patients discharged
			No	%	No	%	No	%	
Day 0	Nil	137							
Day 7	Erythromycin (7)	100/137 (73)	42/100	42	56/100	56*	2/100	2	5/100 (5)
Day 14	Erythromycin (14)	33/57 (58)	22/33	67	11/33	33	0	0	18/33 (55)
	Erythromycin (7) followed by placebo (7)	22/38 (58)	19/22	86	3/22	14	0	0	21/22 (95)
Day 21	Erythromycin (21)	9/15 (60)	6/9	67	3/9	33	0	0	8/9 (89)

*Includes three patients who were isolation-positive on day 7.

size. *H ducreyi* was reisolated from the lesions of three patients in the last group, two of whom had not complied with treatment. In two further patients no improvement was evident, and in one of these the target lesion actually increased in size despite failure to reisolate *H ducreyi*. Pain at the ulcer site was still present, but to a lesser degree, in 32 (32%) cases. On day 7, 57 patients were given a further week's course of erythromycin and 38 patients were given a placebo. Of those patients returning on day 14, no discernible difference in response to treatment was found (table 1). Fifteen patients were given yet a further week of erythromycin treatment and nine (60%) returned on day 21, by which time in all but three the lesions had epithelialised. Overall, there were no treatment failures with erythromycin, since all genital ulcers eventually responded favourably to treatment.

RESPONSE OF ASSOCIATED LYMPHADENOPATHY
Of 91 patients who initially presented with painful lymphadenopathy, 68 (75%) returned for follow up on day 7. Compared with the response of lesions, resolution of associated lymphadenopathy was unsatisfactory, with 57% of lymph nodes showing either no change or deterioration (see table II). Further treatment with erythromycin failed to modify the course of the associated lymphadenopathy.

During the study 26 fluctuant nodes were aspirated to prevent spontaneous rupture. Despite these findings *H ducreyi* was not reisolated from any aspirate or discharging sinus after treatment had started.

SIDE EFFECTS

Side effects of erythromycin were noted in 19 of the 100 patients who returned for follow up examination. Most of these complained of mild abdominal discomfort, but in two cases the side effects were severe enough to warrant discontinuation of treatment after five days; the condition of both these patients had improved and they were discharged without further treatment.

Discussion

This study has confirmed the findings of previous *in vitro* studies that erythromycin is a suitable antimicrobial agent for the treatment of chancroid.^{2,8} In most cases erythromycin treatment resulted in rapid clearance of *H ducreyi* from genital lesions, as reported in Kenya by D'Costa *et al.*,⁹ and also from infected lymph nodes.

Two factors, however, appeared to delay resolution of the disease. Those ulcers which were larger than 20 mm in diameter at initial presentation and

TABLE II Clinical response of chancroid (associated lymphadenopathy) to treatment with erythromycin

			Clinical response of lymphadenopathy to treatment:						
Treatment (duration in days)	No (%) of patients returning		Cured		Improved		Unchanged or worse*		No (%) of patients discharged
			No	%	No	%	No	%	
Day 0	Nil	91							
Day 7	Erythromycin (7)	68/91 (75)	0		29/68	43	39/68	57	3/68 (4)
Day 14	Erythromycin (14)	26/42 (62)	4/26	15	8/26	31	14/26	54	12/26 (46)
	Erythromycin (7) followed by placebo (7)	15/23 (65)	1/15	7	11/15	73	3/15	20	14/15 (93)
Day 21	Erythromycin (21)	9/14 (64)	1/9	11	5/9	56	3/9	33	8/9 (89)

*Includes 26 abscesses which required aspiration during the course of the study.

those that were sited in the coronal sulcus of uncircumcised men were consistently slower to heal. Despite this limitation the rate of resolution of the disease was not dependent on the duration of treatment since an equally good clinical and microbiological response was achieved when treatment was discontinued after one week. Healing could, therefore, possibly occur even after a shorter period of treatment.

The response of the associated lymphadenopathy to treatment is of considerable interest since we detected a similar response in patients treated with co-trimoxazole.¹⁰ Apparently, in many cases, once a certain stage in the process of suppuration of the regional lymph nodes has been reached the natural course of the disease will progress despite effective antimicrobial chemotherapy. Repeated aspiration of the affected glands may be required to prevent spontaneous rupture. The isolation of *H ducreyi* from regional lymph nodes and draining sinuses before treatment and the failure to isolate the causative bacterium after treatment has started indicates a non-infectious mechanism, as does the frequent change in the nature of the aspirate from frankly purulent to serosanguinous after the start of treatment (unpublished observations).

This study has clearly shown that despite considerable clinical experience and adequate laboratory support conditions which present as genital ulcerations may still be misdiagnosed. The finding of two cases of lymphogranuloma venereum and two cases of herpes genitalis serves as a reminder that other conditions may mimic the early lesions of chancroid. The isolation rate of *H ducreyi* from presumed chancroid lesions (142 of 190, 75%) was similar to that previously achieved in Johannesburg and a recent series from Nairobi,¹¹ where a different isolation medium was used. The nature of *H ducreyi*-negative disease remains an interesting subject but may simply reflect the insensitivity of the isolation techniques used, since we found that these cases also responded to antimicrobial agents known to be effective in confirmed cases of chancroid.

Similarly, despite the availability of darkfield microscopy it is often very difficult to determine whether mixed lesions of chancroid and syphilis are present or whether positive serological test results for syphilis in patients presenting with confirmed chancroid indicate previously untreated, inadequately treated, resolved, or resolving treponemal disease.

Although this study has shown that erythromycin given for one week is adequate for successfully treating chancroid, further studies are required to determine the optimum dosage and duration of treatment for achieving satisfactory cure rates. It must be borne in mind, however, that a two week course of this antibiotic would result in the elimination of the causative agents not only of chancroid but also of lymphogranuloma venereum and syphilis.

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